PODCASTMETABOLISM

Science Signaling Podcast: 21 July 2015

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- **Article**
- **Info & Metrics**
- **eLetters**

Abstract

This Podcast features an interview with Cristina Murga and Rocio Vila-Bedmar, authors of a Research Article that appears in the 21 July 2015 issue of *Science Signaling*, about how deleting the kinase GRK2 can counteract some of the metabolic effects of a bad diet. Obesity affects many of the body's normal functions, most notably metabolism. Obesity is associated with insulin resistance and reduced glucose tolerance, which can lead to type 2 diabetes. It also promotes hepatic steatosis, the accumulation of fat in the liver. Vila-Bedmar *et al*. show that deleting *GRK2* can prevent further weight gain and hepatic steatosis and improve glucose sensitivity in obese mice.
Deleting *GRK2* improved these metabolic consequences of high-fat diet–induced obesity even if the kinase was deleted after the mice had already become obese and resistant to insulin.

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Transcript

*Host – Annalisa VanHookWelcome to the Science Signaling Podcast July 21st, 2015. I'm Annalisa VanHook, and today I'm speaking with Rocio Vila-Bedmar and Cristina Murga about how deleting a particular kinase can counteract some of the metabolic effects of a bad diet (**1**).*

Obesity affects many of the body's normal functions, most notably metabolism. Obesity is associated with insulin resistance and reduced glucose tolerance, which can lead to type 2 diabetes. It also promotes the accumulation of fat in the liver, a condition referred to as hepatic steatosis. A new study from Rocio Vila-Bedmar, Cristina Murga, and their colleagues shows that deleting the kinase GRK2 can prevent further weight gain and hepatic steatosis and improve glucose sensitivity in obese mice. Deleting GRK2 improved these metabolic consequences of obesity even if the kinase was deleted after the mice had become obese and resistant to insulin. Murga and Vila-Bedmar spoke to me from Center for Molecular Biology in Madrid.

Interviewer – Annalisa VanHookDr. Murga and Dr. Vila-Bedmar, welcome to the Science Signaling Podcast.

Interviewee – Cristina MurgaHello.

Interviewee – Rocio Vila-BedmarHello.

Interviewer – Annalisa VanHookRocio, we all know that a high-fat diet and obesity have serious metabolic consequences. What are some of the ways in which a high-fat diet and obesity disrupt normal metabolism?

Interviewee – Rocio Vila-BedmarThe effects of a high-fat diet–associated obesity and metabolism are indeed numerous and complex. Actually, white adipose tissue was classically considered a mere storage depot for energy excess, but nowadays it is recognized as an important endocrine organ. In fact, adipocytes are able to modulate global energy homeostasis through the secretion of several factors known as adipokines. This endocrine function partly explains why expansion of adipose tissue may impact whole body metabolism. Moreover, when the storage capacity of adipose tissue is surpassed, it results in lipid accumulation in tissues other than adipose, what is known as ectopic fat deposition. This leads to activation of inflammatory responses, thyroid

dysfunction, and also impaired insulin sensitivity. And all this situation is known as lipotoxicity. Specifically, excessive visceral fat accumulation called central or abdominal obesity is considered causally related to metabolic complications since the enlarged intra-abdominal adipocytes display an increased fatty acid release or increased lipolysis that is resistant to the antilipolytic effect of insulin. This increased lipolysis of visceral fat sends fatty acids into the portal circulation, leading to impaired insulin sensitivity and to increased glucose production in the liver. In addition, this increased flux of free fatty acids contributes to increased triglyceride synthesis and hepatic steatosis.

On the other hand, during obesity, hypertrophic adipocytes shift the immune balance towards the production of proinflammatory molecules that lead to the polarization of the immune cells such as macrophages from an anti- to a proinflammatory state. This conducts to a cell fate cycle of inflammation promoting further macrophage recruitment, and all this proinflammatory state alters the secretion pattern of adipokines, fostering whole body insulin resistance. Moreover, pancreatic β cells try to compensate [for] this systemic insulin resistance [by] increasing insulin production, and this hyperinsulinemic situation, in turn, further stimulates novel lipogenesis in the liver, contributing to the development of hepatic steatosis and complex metabolic dysregulation. Thus, expanded visceral adipose tissue would lead not only to altered fatty acids and triglyceride metabolism, but also to a global proinflammatory profile contributing to the dyslipidemia, insulin resistance, and altered glucose homeostasis that underlie metabolic alterations in obese patients.

Interviewer – Annalisa VanHookCristina, what is GRK2, and why did you focus on its role in metabolic dysregulation?

Interviewee – Cristina MurgaGRK2 is a protein that is capable of incorporating phosphate groups into other proteins. This is why it is called a kinase, and this ability allows GRK2 to control and to regulate the actions of other important proteins in the cell, such as cytosolic effectors and, more importantly, membrane receptors. So, it was previously known that GRK2 could help stop the intracellular signals that emanated from G protein–coupled receptors. However, it was only recently—with our work and that of others—that we could establish that GRK2 can also impair and stop signal transduction triggered by the insulin receptor. So this is a very important issue since insulin is a key metabolic hormone. And this is the main reason why we set out to study whether GRK2 could modify metabolic homeostasis during a whole body response to insulin. We also analyzed how GRK2 can control insulin actions at

the cellular level and also in different tissues important for maintaining body weight and a normal metabolic regulation.

Interviewer – Annalisa VanHookRocio, in this study, you deleted the gene that encodes GRK2 in mice that had already become obese and had already developed insulin resistance as a result of eating a high-fat diet. How does deleting GRK2 affect these mice?

Interviewee – Rocio Vila-BedmarFirst, the global deletion of GRK2 during a high-fat diet impaired body weight again that is classically associated to high-fat feeding and normalized plasma fasting glucose and insulin levels, which are known to be increased in a prediabetic state. Moreover, these mice showed improved glucose tolerance and a more potent activation of insulin signaling and displayed reduced visceral mass and smaller adipocyte size and were resistant to the development of hepatic steatosis and hepatic inflammation. We showed that there seemed to be four processes involved in these beneficial effects of GRK2 deletion: first, improved insulin signaling in peripheral target tissues; second, enhanced lipolysis in white adipose tissue and also in brown adipose tissue; third, increased expression of fatty acid oxidation and thermogenic markers in brown adipose tissue; and finally, reduced steatosis and inflammation in the liver. Such pleiotropic effects of GRK2 are due to both its unique ability to directly modulate the insulin receptor and also to modulate key G protein–coupled receptors related to the control of adiposity in metabolic rates such as β adrenergic receptors.

In part, some of these effects, such as the reduced adipose fat mass or the increased lipolysis found in white adipose tissue, seemed to be related to an enhanced response to adrenergic input. However, the improvement in glucose tolerance prevailed, even under experimental conditions of adrenergic blockade, thus demonstrating that GRK2 loss can influence insulin sensitization independently of its effects on the control of adrenergic signaling. Overall, our data suggest that, either by directly inhibiting the insulin receptor cascade or through the regulation of adrenergic receptors, GRK2 can modulate body weight gain, adiposity, metabolic rates, and downstream targets of the insulin pathway. Under pathological conditions, concomitant increases in GRK2 abundance in several tissues would favor the development of an insulin-resistant phenotype. In contrast, decreases in GRK2 abundance could orchestrate a multiorgan response that would reverse systemic and tissue-specific factors of such insulin resistance and obese phenotype.

Interviewer – Annalisa VanHookCristina, you knocked out the GRK2 gene in your mouse model. Obviously, knocking out a gene is not feasible or advisable in human patients. Could there be other ways to inhibit GRK2 function in obese patients to prevent metabolic disease?

*Interviewee – Cristina MurgaInhibiting GRK2 could have beneficial effect not only for maintaining leanness and for reverting insulin resistance and hepatic steatosis as we showed in this manuscript, but it also would be beneficial in the treatment of cardiac dysfunction, as was demonstrated by the groups of Bob Lefkowitz and Wally Koch and other colleagues (**2**). So, many laboratories have tried along the past decade or so to find an effective and selective inhibitor for GRK2. First, we used peptide inhibitors, and they could bind and maybe impair GRK2 actions, but they were not very effective. And later, we have tried to identify small molecule inhibitors for this kinase without much success. However, it was only this year that the group of Dr. Tesmer has finally described that paroxetine—a well-established inhibitor of serotonin reuptake—can also bind and directly inhibit GRK2 (**3**). We have not been able to use paroxetine in our studies since, apart from inhibiting directly GRK2, it can, of course, affect central nervous system components that are key to metabolic regulation. So, the use of paroxetine would have obscured our results and our conclusions. This is why we had to use genetic ablation of GRK2 as a proof of concept that inhibiting this kinase can, indeed, control weight gain and revert insulin resistance and also hepatic steatosis in a preclinical model, but this was done in the hope [that] more selective inhibitors of GRK2 are developed and available in the near future.*

Interviewer – Annalisa VanHookDr. Murga, Dr. Vila-Bedmar, thanks for speaking with me.

Interviewee – Cristina MurgaWell thank you, it was our pleasure.

Interviewee – Rocio Vila-BedmarThanks to you. Goodbye.

*Host – Annalisa VanHookThat was Cristina Murga and Rocio Vila-Bedmar, discussing a paper published in the July 21st issue of issue Science Signaling by Vila-Bedmar and colleagues (**1**). You can read that article online at stke.sciencemag.org.*

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The Science Signaling Podcast is a production of Science Signaling and the American Association for the Advancement of Science—Advancing Science, Serving Society. If you have any comments or questions, you can write to us atsciencesignalingeditors@aaas.org. I'm Annalisa VanHook, and on behalf ofScience Signaling and AAAS, thanks for listening.

Educational Details

Learning Resource Type: Audio

Context: High school upper division 11-12, undergraduate lower division 13-14, undergraduate upper division 15-16, graduate, professional, general public and informal education

Intended Users: Teacher, learner

Intended Educational Use: Learn, teach

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